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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/938,418	08/23/2001	Avi Ashkenazi	P5009R1	2589

7590 03/14/2006

Attn: Mark T. Kresnak, Ph.D.
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EXAMINER	
SPECTOR, LORRAINE	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 03/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,418	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 15-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date ____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-13 and 15, and newly introduced claims 16-20 are pending and under consideration.

Priority

It is noted that the protein to which the claimed antibodies bind, identified herein as TAT171, but in other applications as PRO866, was shown to induce mouse kidney mesangial cell proliferation and to induce the switch from adult to fetal hemoglobin in PCT US00/04341, which published as WO 00/53756, filed 2/18/00.

Applicants further argue in the paper filed 12/27/2005 that that PCT/US99/05028 (WO99/46281), discloses the use of PRO866 as "an anti-proliferative agent" at page 275, lines 1-23, and provide pager 275, pointing the Examiner to Example 113. This Example is not sufficient to establish priority for the claimed invention, for the following reasons:

he Example discloses, that the PRO866 protein was active, causing at least 50% growth inhibition, against "at least one" of the 60 cell lines of the National Cancer Institute (NCI) anticancerdrug discovery screen (the NCI panel). The asserted utility of the claimed PRO866 protein as a possible chemotherapeutic agent is not considered to be specific, substantial and credible, for the following reasons: Monks et al., Journal of the National Cancer Institute, vol. 83(11):757-766, cited by applicants at page 275 of WO99/46281, disclose and explain the screen itself, including how the screen is performed, and what cell lines are used. The 60 cell lines are independent isolates representing seven distinct types of cancer, namely lung cancer (13 cell lines), renal cancer (9 cell lines), colon cancer (9 cell lines), melanoma (9 cell lines), CNS cancer (8 cell lines), ovarian cancer (6 cell lines), and leukemia (6 cell lines). The WO document merely states that PRO866 tested positive against "at least one" of the cell lines, and does not identify that/those cell lines. It is also noted that the composition of the NCI panel is not static, as Shi et al., referenced below, disclose a different set of 60 cell lines than that disclosed by Monks et al. Therefore, there is no discernable pattern of activity, i.e. the protein does not appear to be active against any particular type of cancer, nor against anything approaching a majority of the cell lines for any given type of cancer. Since PRO866 does not appear to give significant results when tested against the NCI panel, the implicit assertion of utility for the

protein (and by extension nucleic acids encoding such) as an anti-cancer agent is not specific, as such could be asserted for almost any protein, which would be toxic for one or more cell types at some concentration. Further, the implicit assertion of anticancer activity is not substantial. Johnson et al. (Brit. J. Cancer 84(10):1424-1431), in an article entitled "Relationships between drug activity in NCI preclinical in vitro and in vivo models and early clinical trials", state, with regard to the NCI panel that "Agents selected on the basis of potency, selective activity against a particular disease category, and/or differential activity against a few specific cell lines were then evaluated against a small number of sensitive human tumours in the nude mouse xenograft model (citations omitted) as a basis for selecting compounds for further preclinical development. Owing to the large numbers of molecules emerging from the in vitro screen as candidates for xenograft testing, in 1995 this development path was further modified to include a hollow fibre (HF) assay, activity in which was a prerequisite for study in classical xenograft models" (page 1424, second column). Thus, the initial screen against the 60 cell lines of the NCI panel is not considered by the art to be predictive of *in vivo* activity against tumors, and, as characterized by Johnson et al., such is merely the first of a three-part protocol for identification of agents to be tested in vivo. Further, Shi et al., (J. Chem. Inf. Comput. Sci. 40:367-379), clearly state that "Although cell growth inhibitory activity for a *single* cell line is not very informative, activity *patterns* across the 60 cell lines can provide incisive information on the mechanisms of action of screened compounds...." (abstract). The paper, drawn to methods of mining and visualizing the large amounts of data generated by the NCI panel, further states that relative activity levels distinguish better among the tested cell lines than do the GI_{50} activity patterns, and that "The mean zero preprocessing procedure seemed to eliminate the noninformative "inherent" cytotoxicity, thus brining out the informational differential cell responses (p. 377, end of first column). Thus, Shi et al. indicates that the art does not consider the raw GI_{50} data are insufficient to identify compounds that are likely to be antitumor candidates to be tested further. Further, Shi clearly indicates that testing positive against a single cell line would not be considered significant. Finally, Brown (Oncology Research, 1997) tested a subset of the NCI cell lines for cell kill using cisplatin and mitomycin C and found only "a weak and nonsignificant correlation between cell kill and activity determined by the NCI using the growth inhibition assay." (Abstract.) The title of the article, "NCI's anticancer drug screening program may not be

selecting for clinically active compounds", clearly indicates that the NCI panel is not considered to be predictive of *in vivo* utility.

Accordingly, the implicit assertion of utility as an anti-cancer agent is not substantial, as the art does not support that mere identification of killing of "at least one" of the 60 NCI panel cell lines would be predictive of anti-tumor activity, and thus would not constitute a substantial and credible utility for PRO866.

Accordingly, priority to that application is *denied.*

In view of the above, priority for this application remains set at 2/18/2000.

Rejections over Prior Art

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-9, 12-13 and 15 remain, and newly submitted claims 16-20 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Number 6,682,902 (Harkins et al.) for

reasons cited in the previous Office Action. The Harkins patent merits priority to the filing date of application 60/172,370, filed 12/16/1999. Applicants arguments regarding priority date are not persuasive for reasons cited above.

Claims 1-9, 12-13 and 15 remain, and newly submitted claims 16-20 are rejected under 35 U.S.C. 102(b) as being anticipated by WO98/45442 (Sheppard et al., cited by applicants) for reasons cited in the previous Office Action. Applicants arguments regarding priority date are not persuasive for reasons cited above.

Claims 1-8, 12-13 and 15 remain, and newly submitted claims 16-20 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Number 5,871,969 (Hastings et al., cited by applicants). The Hastings patent merits priority to at least 2/12/1997. This rejection is maintained for reasons of record.

Applicants argue at page 6 of the response filed 12/27/05 that the recitation that the antibody "specifically binds" excludes any cross-reactivity. This argument has been fully considered but is not deemed persuasive because the term "specifically binds" is not the same as "exclusively binds". It is well known in the art that an antibody that binds to a given sequence in one protein will bind to that same sequence in another protein that comprises the sequence. Hastings discloses a protein designated human neuronal attachment factor-1 (NAF-1), which is 98.9% identical to SEQ ID NO: 8. The vast majority of antibodies to Hastings' protein would "specifically bind" to the protein of SEQ ID NO: 8, as the vast majority, if not all, of the epitopes in the two proteins are identical. Applicants have provided no argument, fact, evidence, or scientific evidence to support their argument that the antibodies of Harkins would not meet the metes and bounds of the claims.

Claims 1-8, 12-13 and 15 remain, and newly introduced claims 16-20 are, rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Number 6,287,777 (Sytkowski et al., cited by applicants). The Sytkowski patent merits priority to at least 8/10/1999. Applicants arguments regarding priority date are not persuasive for reasons cited above.

Claims 1-8, 12-13 and 15 remain, and newly introduced claims 16-20 are rejected under 35 U.S.C. 102(a) as being anticipated by WO99/46281 (Wood et al., cited by applicants). Applicants arguments regarding priority date are not persuasive for reasons cited above.

Claims 1 and 2 remain, and newly introduced claims 16-20 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Higashijima et al., Developmental Biology 192:211-227, 1997. Higashijima et al. disclose production of polyclonal antibodies using a peptide corresponding to residues 188-202 of SEQ ID NO: 8 of this application. Accordingly, the claims are anticipated.

Applicants argument pertaining to the recitation "specifically" has been fully considered but is not deemed persuasive for reasons cited above. Further, a *prima facie* case of inherency has been made. As Wood raised antibodies to a fragment of SEQ ID NO: 8, and as it is well known in the art, and indeed disclosed in the instant specification, that fragments of proteins may be used to raise antibodies to a given protein, it is clearly inherent that Wood's antibodies would meet the limitations of the claims. As the state of the art would lead one to expect this, the burden is shifted to applicants to establish by fact or evidence, that such would not be expected to be the case. Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10 and 11 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Harkins or Sheppard, either one in view of U.S. Patent Number 5,208,020 (Chari et al.).

Claims 10 and 11 contain the limitation that the toxin to which the claimed antibody is conjugated is a maytansinoid, or calicheamicin. Each of the primary references teach the claimed antibodies conjugated to a toxin, but do not specifically teach either of these two toxins.

Chari et al. disclose and claim a cytotoxic agent comprising one or more linked to a monoclonal antibody (see, e.g. claim 1). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute maytansinoids as the toxin in the antibody/toxin conjugates of any of the primary references for their known and expected properties, as taught by Chari et al. Accordingly, the invention, taken as a whole, is *prima facie* obvious.

Applicants argument has been fully considered but is not deemed persuasive for reasons cited above.

Claims 3-9, 12-13 and 15 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Higashijima et al., Developmental Biology 192:211-227, 1997 in view of Lal et al., U.S. Patent No. 5,932,445.

Lal is cited as evidence that production of monoclonal, chimeric, and isotope-labeled antibodies was notoriously old and routine in the art at the time the invention was made. Monoclonal and polyclonal antibodies are disclosed at the paragraph bridging columns 20-21. Further discussion of antibodies, including monoclonal, polyclonal and single chain and humanized antibodies, as well as radioactively labeled antibodies, is found at column 24-25. Accordingly, the invention as claimed is anticipated by Lal et al. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the antibodies of Higashijima by making monoclonal, fragment, chimeric, radioactive and labeled antibodies as taught by Lal et al. as being routine in the art at the time the invention was made, to attain the known and art-recognized advantages of such, as taught by Lal et al. . One would have been motivated to do so to obtain homogeneous and useful reagents for the immunohistology performed by Higashijima et al. Accordingly, the claims, taken as a whole, are *prima facie* obvious over Higashijima et al., in view of the state of the art as evidenced by Lal et al.

Applicants argument has been fully considered but is not deemed persuasive for reasons cited above.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

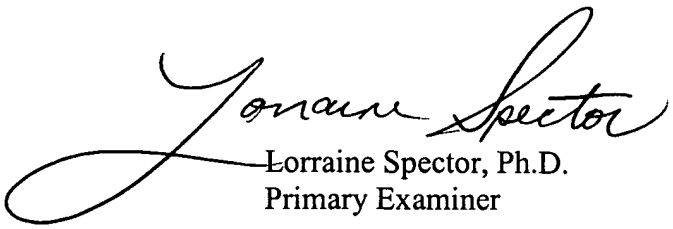
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. ***Effective 1/21/2004, Dr. Spector's telephone number is 571-272-0893.***

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Lorraine Spector, Ph.D.
Primary Examiner

3/8/2006